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ORO-GENITAL APHTHOSIS*

BY

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Whilst superficial ulceration of either the oral or the genital mucosa is common, *concurrent* ulceration of those two sites with added eye involvement is relatively rare. The first recorded instance of this triad of symptoms is found in Hippocrates' Third Book of Endemic Diseases written in the 5th century B.C. (Adams, 1849). From the same area of the Eastern Mediterranean, Behçet (1937) described a clinical syndrome, the main features of which showed a remarkable resemblance to those noted by the priest-physician 24 centuries previously. Since then, further cases of oro-genital ulceration have been described by workers in other lands and various names have been given to clinical entities which showed a *close* similarity to one another—although the sequelae were sometimes different. To add to the confusion, no definite causative agent has been identified, although recent work by Sezer (1953) seems to support Behçet's original claim that the syndrome which bears his name is possibly of virus origin. Sezer claims to have isolated a causative virus from the posterior chamber of an enucleated eye. A further pointer in the same direction was provided by Evans, Pallis, and Spillane, (1957), who obtained a similar virus from the brain of a patient who had developed Behçet's disease with fatal neurological involvement. Despite this, differential diagnosis remains a matter of great difficulty, is often conjectural, and is necessarily retrospective.

Case Reports

Clinical Features.—Table I (opposite) shows the salient clinical features of three cases of oro-genital ulceration seen in the Venereal Diseases Department at the Royal Infirmary, Edinburgh, during the past 4 years. The initial lesions all appeared within the buccal cavity and were either vesicular or bullous. The mucosa of the lips, cheeks, gums, fauces, and tongue were affected. Within 24 hours the vesicles ruptured, leaving superficial craters with whitish-yellow bases and reddened but not raised margins. The intervening mucosa was apparently healthy and the regional glands were not enlarged. The genital lesions appeared 2 or 3 days later and resembled the oral lesions in appearance and behaviour.

The external urinary meatus was implicated in the disease process.

In one patient only scrotal ulceration was present. The cutaneous lesions, which appeared about the same time, were sparse and pustular, and affected either the forehead or the forearms.

Investigations.—These are shown in Table II (opposite). In addition, periodic complement-fixation tests using appropriate virus antigen were carried out on the patients' sera. No significant rise in antibody titre was noted. Biopsy examination of the oral and genital lesions showed neither inclusion bodies nor any other specific pathological picture. Other findings were negative, although the blood sedimentation rate was raised in the pyrexial patients. All three showed a moderate leucocytosis but no distinctive pattern emerged in the differential blood count.

Treatment.—Before admission to hospital all three patients had had a full course of tetracycline hydrochloride without apparent effect. The treatment given in hospital was purely palliative (Table III, overleaf). Accurate assessment of these various forms of treatment is impossible since oro-genital ulceration can run a short, self-limiting course. However, the hydrocortisone pellets alleviated the pain of the oral lesions to a remarkable extent and these lesions were always the first to heal. It is debatable whether this was due to the local steroid therapy or was a part of the natural course of the disease.

Results.—The first two patients became asymptomatic less than 3 weeks from the start of their illness and have since remained so, the first having been followed up for 4 years and the second for 3 months. In the third patient relapses are still occurring after 9 months, the same sites being repeatedly involved.

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TABLE I
SUMMARY OF SIGNS AND SYMPTOMS

Case No.			I	II	III
Age (yrs)			17	19	21
Occupation			Apprentice Engineer	Apprentice Engineer	Policeman
Marital Status			Unmarried	Unmarried	Unmarried
Last Sexual Exposure			2 weeks previously	5 months previously	None admitted
First Appearance of Symptoms			1 week previously	1 week previously	5 months previously
Temperature; Pulse; Respiration			101·4°F.; 82; 22	101·6°F.; 80; 18	98·4;F.; 72; 16
Symptoms			Painful mouth and throat Head cold and cough Inflammation of penis with profuse subpreputial discharge	Painful mouth and throat Head cold and cough Blisters on penis	Painful mouth and throat — Scrotal ulceration
Lesions	Oral	Lips Tongue Fauces	++ + ++	++ + ++	++ — +++
	Genital	Glans Prepuce Scrotum	++ + —	+ + —	— — ++++
	Cutaneous		Sparse on forearms	Sparse on forehead	Extensive on Scrotum
	Conjunctival		Mild	—	—
Date of Admission to Hospital			August 9, 1961	February 17, 1965	Treated as out-patient (for social reasons) February 20, 1965

TABLE II
RESULTS OF INVESTIGATIONS UNDERTAKEN

Case No.		I	II	III
Blood Sedimentation Rate (Westergren) (mm./1 hr.)		28	40	8
Haemoglobin (per cent.) Red Blood Count (m./c.mm.)		100 5	98 4·8	109 5
Blood Film		Normal appearance	Normal appearance	Normal appearance
White Blood Count		14,500	12,400	13,000
Differential Count (per cent.)	Neutrophils Lymphocytes Eosinophils Monocytes	67 22 8 3	71 17 3 9	63 27 4 6
Standard Tests for Syphilis		Negative	Negative	Negative
Dark-Ground Investigations		Negative	Negative	Negative
Oral Smears and Cultures		β-haemolytic streptococci and commensals	Diptheroids Scanty yeast mycelia	Respiratory commensal organisms
Genital Smears and Cultures		*Staphylococcus albus* Diphtheroids	Diphtheroids	Micrococci only
Vincent's Organisms		Not found	Not found	Not found

Discussion

The main interest in these cases lies in the problem of differential diagnosis. The clinical conditions requiring differentiation fall conveniently into two main groups:

Group A

Conditions which can be excluded with reasonable certainty (Table IV, overleaf).

Varicella.—The occurrence of the lesions of chickenpox upon sites identical to those affected in

TABLE III
TREATMENT SCHEDULES

Case No.	I	II	III
Oral Lesions	Hydrocortisone pellets 2·5 mg. 1 four times daily	Hydrocortisone pellets 2·5 mg. 1 four times daily Metronidazole tabs. 200 mg. 1 three times daily	Hydrocortisone pellets 2·5 mg. 1 four times daily
Genital Lesions	Eusol subpreputial washouts Gauze strip dressing Pad and T bandage	Eusol subpreputial washouts Gauze strip dressing	Eusol subpreputial washouts Gauze strip dressing Terracortril spray four times daily
Systemic Treatment	Betamethasone tabs. 2 mg. for 3 days, thereafter 1 mg. for a further 5 days	Parentrovite 7 ml. intramuscularly twice weekly	Parentrovite 7 ml. intramuscularly twice weekly

TABLE IV
DIFFERENTIAL DIAGNOSIS—GROUP A
CONDITIONS EXCLUDED ON FOLLOWING GROUNDS .

Clinical	Bacteriological	Serological	Haematological
Exanthemata Reiter's syndrome Acute herpetic infection Pemphigus	Vincent's angina Thrush	Syphilis	Blood dyscrasias

our patients is not uncommon. However, the patients had all had varicella in childhood and had had no contact with known cases, and the rash did not appear in crops. Furthermore, chickenpox did not occur amongst any of the close contacts of the patients.

Reiter's Syndrome.—Initially some of the signs suggested the possibility of an incipient Reiter's syndrome (Reiter, 1916). However, there was never any joint involvement even of a transient nature and the rapid complete clinical recovery in two of the patients ruled out this diagnosis.

Acute Herpetic Infection.—When widespread, this condition can cause severe if evanescent constitutional symptoms with vesicular and ulcerative lesions affecting the oro-genital mucosa. Recurrences are frequent. In our patients, no eosinophilic inclusion bodies were demonstrated in the epithelial cells, nor was there any significant rise in antibody titre in their sera.

Pemphigus.—Our patients never showed the chronicity or toxicity which is such a feature of this condition.

Vincent's Angina and Thrush.—Extensive ulceration of the mucosa of the mouth and genitalia can occur simultaneously in both these conditions. (Harkness, 1950). However, repeated examination failed to demonstrate *Monilia albicans*, *B. fusiformis*, or *Borrelia Vincenti*.

Syphilis.—This, in its acute form, was the initial tentative diagnosis in all three patients. However, dark-field investigation of the oral and genital lesions showed no *T. pallidum*, and standard serological tests for syphilis remained negative throughout a lengthy period of observation.

Group B

Conditions in which the clinical appearances are so similar that absolute differentiation is extremely difficult if not impossible (Table V, opposite).

In France, Fiessinger and Rendu (1917) published a series of cases in which aphthous ulceration appeared on the mucous membranes of the oral and genital regions with accompanying conjunctivitis. This condition was called "ectodermose érosive pluriorificielle". A few years later in America, Stevens and Johnson (1922) described a condition which showed all the salient features of the foregoing—although in a more severe form. Since then, numerous names have been applied by workers in different lands to syndromes with very similar behaviour patterns and differences often more apparent than real. Close study suggests that these may all be clinical variants of the same condition. Several workers have suggested that much confusion would be avoided if Hebras' (1866) original title "erythema multiforme exudativum" was used to cover the basic clinical picture.

TABLE V

DIFFERENTIAL DIAGNOSIS—GROUP B

Disease	Characteristic Features
(1) Ectodermose erosive pluriorificielle (Fiessinger and Rendu, 1917, Paris) (2) Dermatostomatitis (3) Eruptive fever with stomatitis and ophthalmia (Ginandes, 1935, U.S.A.) (4) Stevens-Johnson syndrome (Stevens and Johnson, 1922, U.S.A.) (5) Erythema multiforme exudativum (Hebra, 1866)	1. Abrupt febrile onset 2. Frequent involvement of respiratory tract 3. Superficial ulceration of mouth, tongue, and fauces 4. Genital mucosal ulceration involving external urinary meatus 5. Catarrhal conjunctivitis 6. Sparse macular, papular, or pustular skin lesions 7. Self-limiting course of 2 to 3 weeks' duration 8. Recurrence rare
Behçet's syndrome (Behçet, 1937, Istanbul)	1. Apyrexial onset 2. Respiratory tract involvement unusual 3. Oro-genital ulceration, tongue rarely implicated 4. Scrotal ulceration frequent 5. Serious eye involvement often with subsequent visual deterioration 6. Chronic relapsing course 7. Sometimes serious features, *e.g.* recurrent thrombophlebitis, arthritis, and involvement of central nervous system. 8. Occasional abortive forms with incomplete clinical picture (Curth, 1946).

In Istanbul, Behçet (1937) published the first of a series of papers describing the condition which now bears his name. Oro-genital ulceration with simultaneous involvement of the eye is once again a feature.

However, there are a number of important differences. Behçet described a chronic relapsing condition with frequent involvement of the internal structures of the eye—visual deterioration being common. These findings have been amplified by later workers (Knapp, 1941), who included other associated symptoms within the syndrome, recurrent thrombophlebitis, arthritis, and involvement of the central nervous system being some of the more serious. The whole picture is one of a very severe disease; The eye may often emerge unscathed from the earlier attacks although it is invariably involved in one of the later relapses. Recognizing this, Curth (1946) claimed that the syndrome may be *suspected* in a patient who does not initially satisfy *all* the diagnostic criteria, *e.g.* if only two of the triad of symptoms are present. Final judgment is necessarily retrospective.

Conclusions

There is a close similarity between the first two patients, both of whom were pyrexial and had sore mouths and an upper respiratory tract infection. The oro-genital lesions were almost identical in distribution, intensity and appearance. The illness was of short duration and has not recurred. It is this freedom from relapse which sustains our belief that these patients belong to the erythema multiforme exudativum group—as probable examples of the Stevens-Johnson syndrome.

The third patient, who had an afebrile illness with extensive oral and scrotal ulceration, continues to relapse after a period of 9 months, but so far, there has been no ocular inflammation. Tentatively we regard this third patient as a possible example of the incomplete Behçet's syndrome; time alone will prove the accuracy of this view.

Summary

(1) The salient clinical features of oro-genital ulceration occurring in three young male patients are described.

(2) Two of these patients showed a striking similarity in history and clinical appearances, the site, distribution, appearance, intensity, and duration of the oro-genital lesions being almost identical. In the third patient there were clinical differences which may be significant.

(3) The difficulties of differential diagnosis are stressed.

(4) It is suggested that, in the present state of our knowledge, long-term surveillance is necessary before a final diagnosis can be reached.

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Aphtes orogénitaux

RÉSUMÉ

(1) On décrit les traits cliniques dominants produits par des ulcérations orogénitales chez trois jeunes hommes.

(2) Chez deux de ces malades l'histoire et les symptômes cliniques se ressemblèrent étonnamment, le lieu, la répartition, l'apparence, l'intensité et la durée des lésions orogénitales étant presque identiques. Chez le troisième il y eut des différences cliniques peut-être significatives.

(3) On insiste sur la difficulté du diagnostic différentiel.

(4) On suggère que dans l'état actuel de nos connaissances une surveillance prolongée est nécessaire avant qu'un diagnostic définitif puisse être atteint.